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ABSTRACT

Prepared as a resource for developing a 5-year plan of research for the years 1983-1987 by the National Institute of Child Health and Human Development, this report reviews current knowledge in three areas of perinatal medicine: pregnancy, birth, and the infant. Within each of these three general areas, several subtopics are discussed. These subtopics include various maternal disorders during pregnancy, fetal distress and hypoxic birth injury, and the respiratory distress syndrome in premature infants. The concluding section of the document offers recommendations for future research. (Author/RH)

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Child Health and Human Development

An Evaluation and Assessment of the State of the Science

Pregnancy, Birth, and the Infant

PS 012841

Foreword

This report is one of ten prepared in 1980 for the Steering Committee for the Five-Year Research Plan of the National Institute of Child Health and Human Development (NICHD). In developing the plan, a Study Group for each of the ten NICHD program areas was asked to evaluate the state of the science, identify areas of promise, and recommend directions for future research. Each Study Group consisted of leading scientists and staff of the NICHD. The Steering Committee conducted an extensive scientific and policy review of the reports, and collected and published them in Child Health and Human Development: An Evaluation and Assessment of the State of the Science (October 1981). The reports reflect specific interests and expertise of the authors and not necessarily NICHD policy. The report on the following pages is reprinted from the collection. The ten program areas are:

I Fertility and Infertility
II Pregnancy, Birth, and the Infant
III Nutrition
IV Sudden Infant Death Syndrome
V Congenital Defects
VI Mental Retardation
VII Child and Adolescent Development
VIII Contraceptive Development
IX Contraceptive Evaluation
X Population Dynamics

Each program area will be reviewed and updated annually as part of the NICHD planning and evaluation process. By this means, areas not emphasized adequately can be addressed, the guidance of other experts can be sought, and changes in the state of the science and changes in health issues can be accommodated.

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Pregnancy, Birth, and the Infant

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Pregnancy, Birth, and the Infant

I. Introduction

Of all phases of the human life cycle, pregnancy and childbirth have been accorded a favored status by society. This focus on pregnancy, birth, and the infant carries over to medicine as well, and the field of maternal and infant health has been especially singled out in biomedical science in an effort to preserve life and improve its quality. The events of pregnancy, labor, and birth are the major determinants of lifetime well-being. Diagnosis and treatment of a disease on the first day of life, which is the most hazardous any individual experiences, may determine whether there is a cure, an early death, or a lifelong disability.

One consequence of the focus on pregnancy and childbirth has been the collection of relevant medical statistical data. National, regional, and local data provide reliable indices of improvements in the health of pregnant women and their infants, and the data from 1970 to 1978 (the most recent year for which final figures are available) show:

- a decrease of 55.3 percent in the maternal mortality rate, from 21.5 deaths per 100,000 live births to 9.6, the lowest rate in history;

- a decrease of 31 percent in the infant mortality rate (deaths in the first year of life), from 20 deaths per 1,000 live births to 13.8, also the lowest rate ever;* and

*1980 estimated rate: 12.5

- a decrease of 37.1 percent in the neonatal mortality rate (deaths in the first 28 days of life), from 15.1 deaths per 1,000 live births to 9.5, again the lowest rate ever.

These improvements are largely a result of the clinical application of knowledge gained through research, combined with wider access to health care.

A number of research advances contributed to these improvements and also to the reduced long-term morbidity of the survivors. Continuous positive airway pressure (CPAP), developed to prevent the collapse of small airways in hyaline membrane disease/respiratory distress syndrome, helped reduce the number of deaths caused by this disorder from 9,763 in 1970 to 5,991 in 1978, and the combination of CPAP and other techniques for improved management of very low birthweight infants (less than 1,500 grams) in newborn intensive care units approximately doubled their survival rate. Intrauterine diagnosis has enabled many families to have children unaffected by genetic disease and congenital defects and has permitted initial applications of intrauterine therapy for some of them. The administration of Rh immune globulin (RhoGam) to Rh negative women after delivery, to prevent sensitization and development of erythroblastosis fetalis in subsequent pregnancies, has reduced the incidence of affected newborns per 1,000 births from 4.1 in 1970 to 1.6 in 1977. The development and application of the methodology for simple, inexpensive, universal screening of newborns for congenital hypothyroidism have provided the means for completely preventing this cause of mental retardation. With the development of tests for fetal lung maturity and of means for in utero treatment to stimulate lung maturation, the problem of respiratory distress syndrome due to cesarean delivery performed too early and its incidence in women with premature labor have been significantly reduced.

The declines in maternal and neonatal mortality have also been influenced significantly by the availability of safe and effective contraceptives and by broader use of regionalized special perinatal care facilities.[1]

In spite of these advances, over 45,000 infants die each year in the United States. Infant mortality rates are lower in 13 other countries. The U.S. prematurity rate remains high. This is the major reason why the infant mortality rate is not considerably lower. Questions of

management of pregnancy-induced hypertension, diabetic pregnancy, and difficult labor are unresolved, and infections and congenital anomalies take a high toll and often leave survivors disabled for life.

The most striking record of improvement is the decline of maternal mortality. At the turn of the century, 1 percent of pregnant women could expect to die of complications of pregnancy, labor, and delivery within 6 weeks postpartum. As recently as 1930, nearly 15,000 women died in 2.2 million births (table 1). By 1978, only 321 women died in 3.3 million births--less than 1 in 10,000. The rate has declined 100-fold in 60 years. Comparison of the causes of maternal death in 1970 and 1978 (table 2) suggests areas of progress and indicates future needs.

Infant mortality also shows a striking decline in this century, but of a different order of magnitude. While maternal mortality has been reduced 100-fold, infant mortality has declined not quite 10-fold (table 3). In recent years, most of the decline has been in the neonatal period (the first 28 days of life). An examination of the leading causes of infant death and the changes in them since 1970 (table 4) indicates where special problems remain. Only minor progress, for instance, has been made against congenital anomalies, still the major cause of both mortality and disability. By contrast, marked improvements in rates have occurred for pneumonia (72.8 percent reduction), hyaline membrane disease (HMD) (43.7 percent reduction), and respiratory distress syndrome (RDS) (16.6 percent reduction).*

Marked improvement in the ability to keep very low birthweight infants alive has resulted from many changes in management, and is demonstrated in the 53 percent reduction in mortality attributed to immaturity. The death rate from asphyxia of the newborn declined by 65 percent, largely as a result of increased application of electronic fetal monitoring during labor in high-risk patients, apnea monitoring in nurseries, and improved resuscitative and supportive techniques. Similarly, there was a 62.4 percent reduction in death rate due to conditions of the placental pathology. Sepsis was the only condition that showed a rise in mor-

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*For statistical purposes, based on International Classification of Diseases Adapted codes, RDS and HMD are considered separately. Elsewhere in this document they are considered together under the more general term respiratory distress syndrome.

tality rate, indicating an increasing problem of neonatal sepsis due to Group B streptococci.

Prematurity--whether it is defined as low birthweight (less than 2,500 grams), preterm delivery (less than 37 weeks gestational age), or both--is a common factor of many of these figures. Four of the six leading causes of death (immaturity, RDS/HMD, and asphyxia), which comprise over one-fourth of all infant deaths, are confined almost entirely to premature infants. Furthermore, all the rest of the leading causes, with the possible exception of accidents, are more common in premature infants. Nationwide, approximately 60 percent of all infants who die in the first year weigh less than 2,500 grams at birth, and in some geographic areas this proportion is much higher. Infants weighing less than 1,500 grams constitute only 1 percent of all live births, but approximately two-thirds of all neonatal deaths.[2]

Premature infants are not only more likely to die; they are also more likely to suffer long-term morbidity as a consequence of these disorders and of intracranial hemorrhage. Although it is much more difficult to obtain data on morbidity than on mortality, it is clear that the risk for handicap rises as birthweight declines. Among infants weighing less than 1,500 grams, the incidence of handicap ranges upward from 10 percent[3] and has been reported to approach 60 percent at 8 years of age.[4] Costs associated with these problems are high. A 1978 study indicated an average cost of over $8,000 for intensive care for each premature infant, or an annual hospital cost alone of over $1.5 billion.[5] To this figure must be added the unknown long-term costs of caring for the physical and mental handicaps of many of those who survive.

National data on prematurity based on birthweight have been available only since 1950, and they demonstrate comparatively little progress, even though the current prematurity rate of 7.1 percent is the lowest yet recorded (table 5). While the rate has fluctuated, there has been essentially no change in nearly 30 years. This rate is not the biologic limit: the rate in Sweden is 3.9 percent; in New Zealand, 5.2 percent; in Japan, 5.3 percent. Further improvement in the United States is possible. The rate of prematurity among non-whites was 12.8 percent in 1977 and was more than double the rate of 5.9 percent among whites. This difference is due in part to differences in prenatal and perinatal care, reflecting social, economic, and educational environment.

The potential to improve infant survival in the United States by lowering the prematurity rate is indicated in a recent study by the World Health Organization.[6] A valid index of health care is perinatal mortality, or the total number of fetal deaths from 28 weeks gestation to birth, plus infant deaths from birth through 28 days of age. These measures largely reflect the quality of medical care, and are relatively less influenced by social factors. When crude perinatal mortality rates are examined (1973 data), the United States does relatively better than in infant mortality, but still trails the leader, Sweden (table 6). Sweden, however, had only a 3.9 percent prematurity rate in 1973, compared to 7.6 percent in the United States. The importance of this difference becomes apparent when birthweight-specific rates are compared (table 7). For each birthweight group from 500 to 3,500 grams, perinatal mortality is lower in the United States than in Sweden or any other country studied. Perinatal mortality calculated in a way to adjust for the difference in birthweight indicates that the United States, not Sweden, has the lowest perinatal mortality rate when standardized on a weight-adjusted basis (table 6). Thus, the care pregnant women and newborns receive in the United States is the best in the world for achieving newborn survival and not 14th best, as has been claimed. The implication, however, is clear: if overall U.S. infant mortality is to be reduced and the world rank is to be improved, the first priority in research and patient care must be to lower the prematurity rate.

TABLE 1. Maternal Mortality, United States, 1920-1979

Year	Number of Maternal Deaths	Maternal Mortality Rate (Deaths per 100,000 Live Births)
1920	N.A.	799.0
1930	14,833	673.0
1940	8,874	376.0
1945	5,668	207.2
1950	2,950	83.3
1955	1,901	47.0
1960	1,575	37.1
1965	1,189	31.6
1970	803	21.5
1977	390	11.2
1978	321	9.6
1979	270 (Provisional)	7.8

Compiled from National Center for Health Statistics data

TABLE 2. Maternal Deaths and Mortality Rates, United States, 1970 and 1978

Rank (1978)	Cause of Death	Number of Maternal Deaths 1970	Number of Maternal Deaths 1978	Maternal Mortality Rate (Deaths per 100,000 Live Births) 1970	Maternal Mortality Rate (Deaths per 100,000 Live Births) 1978
1	Toxemia	142	62	3.8	1.9
2	Sepsis	144	61	3.9	1.8
3	Ectopic pregnancy*	63	37	1.7	1.1
4	Hemorrhage*	86	36	2.3	1.1
5	Abortions	128	16	3.4	0.5
6	Other	240	109	6.4	3.2
	TOTAL	803	321	21.5	9.6

Compiled from National Center for Health Statistics data

*Many of the deaths from ectopic pregnancy could be combined with those from hemorrhage, which is the usual cause of death in ectopic pregnancy.

TABLE 3. Infant Mortality Rate, United States, 1915-1980

Year	Rate (Deaths per 1,000 Live Births)
1915	99.9
1930	64.6
1940	47.0
1950	29.2
1960	26.0
1965	24.7
1970	20.0
1974	16.7
1978	13.8
1979	13.0 (Provisional)
1980	12.5 (Provisional)

Compiled from National Center for Health Statistics data

TABLE 4. Deaths Under 1 Year and Infant Mortality Rates, United States, 1970 and 1978

Rank (1978)	Cause of Death	Number of Infant Deaths		Infant Mortality Rate (Deaths per 100,000 Live Births)	
		1970	1978	1970	1978
1	Congenital anomalies	11,259	8,404	301.7	252.1
2	Sudden infant death syndrome	Not coded	4,963	Not coded	148.9
3	Immaturity, unqualified	8,752	3,677	234.6	110.3
4	Respiratory distress syndrome	4,459	3,324	119.6	99.7
5	Asphyxia of newborn	9,438	2,955	252.9	88.7
6	Hyaline membrane disease	5,304	2,667	142.1	80.0
7	Birth injury	2,150	1,851	57.6	55.5
8	Influenza and pneumonia	6,303	1,533	168.9	46.0
9	Accidents	2,294	1,262	61.5	37.9
10	Septicemia	865	1,093	23.2	32.8
11	Conditions of placenta	2,281	768	61.1	23.0
12	All other	21,562	13,448	577.9	403.5
	TOTAL	74,667	45,945	2,001.1	1,378.4

Compiled from National Center for Health Statistics data

TABLE 5. Prematurity Rate (Birthweight <2,500 Grams), United States, 1950-1977*

Year	Percent Premature
1950	7.6
1955	7.6
1960	7.7
1965	8.3
1970	7.9
1974	7.4
1977	7.1

Compiled from National Center for Health Statistics data

*No national data obtained before 1950

TABLE 6. Perinatal Mortality Rates,* Observed and Standardized for Birthweight, United States and Other Countries

Country	Crude Rate	Rank	Standardized Rank	Rank
Sweden	12.6	1	14.5	2
United States	14.9	2	11.7	1
Japan	17.0	3	18.9	5
New Zealand	17.3	4	17.3	3
Austria	21.4	5	18.2	4

Source: World Health Organization[6]

*Perinatal deaths per 1,000 live births

TABLE 7. Perinatal Mortality Rates* by Birthweight, United States and Other Countries

Country	Perinatal Mortality Rate <2,500 Grams	Perinatal Mortality Rate ≥2,500 Grams
Sweden	197.1	5.2
United States	141.9	4.6
Japan	174.7	8.1
New Zealand	201.9	7.0
Austria	243.9	7.8

Source: World Health Organization

*Perinatal deaths per 1,000 live births

II. Pregnancy

Maternal Medical Disorders During Pregnancy

The growing fetus is totally dependent on the mother during pregnancy, and maternal diseases or nutritional problems during gestation can have a major impact on the fetus. Some of these conditions, such as maternal rubella, have been thoroughly studied. Their effects have been well documented and effective means of prevention have been developed. Others, such as pregnancy-induced hypertension, have been studied extensively, but their pathogenesis and effects on the fetus are less well understood, and their treatment, although effective, is largely symptomatic. Recently, such conditions as maternal genito-urinary infections have been identified as possible causes of fetal problems. For some fetal abnormalities and for congenital defects in particular, such as limb deformities, a causative maternal disorder or exposure to a foreign agent is suspected, but the source has not yet been determined.

Hypertensive Disorders in Pregnancy

Hypertensive disorders in pregnancy include pregnancy-induced hypertension (preeclampsia and eclampsia), chronic (preexisting) hypertension, transient hypertension, preeclampsia superimposed on chronic hypertension, and other hypertensive disorders. Their combined incidence is 6 to 8 percent of all pregnancies, although there are geographic, temporal, racial, and possibly socioeconomic variations.[7]

The disorders predispose to cerebral hemorrhage, abruptio placentae, acute renal failure, circulatory collapse, disseminated intravascular coagulation, and other complications. They are a major cause of maternal, fetal, and neonatal morbidity and mortality, and in some parts of the world, including the United States, they are the leading cause of maternal death. Nationwide, they account for two maternal deaths per 100,000 births. Fetal growth may be affected adversely, and the perinatal death rate ranges from 4 to 38 percent, depending upon the severity of the disease.[8-10] A significant proportion of surviving infants have neurologic and developmental defects.

Hypertensive disorders are often diagnosed inaccurately and at times are difficult to distinguish from each other. Most research has been directed toward pregnancy-induced hypertension (preeclampsia-eclampsia). Preeclampsia is the development of hypertension together with abnormal edema or proteinuria, or both, after the 20th week of gestation. It is rare before the 24th week, unusual before the 30th, and increasingly common as pregnancy approaches term. In some women it progresses to eclampsia, which is preeclampsia plus convulsions not attributable to identifiable causes. Preeclampsia is predominantly a disease of primigravidas, and the diagnosis usually is erroneous in multiparas. Its underlying cause is unknown, and its treatment is symptomatic, though generally effective.[11,12]

Many tests have been proposed to predict which women will develop preeclampsia, but none have been conclusive. The refractoriness to the pressor effect of angiotensin II, characteristic of normal pregnancy, is lost progressively over a period of many weeks before any clinical sign of preeclampsia. This loss of refractoriness suggests that vascular sensitization is an early abnormality.[13] The hitherto supernormal placental clearance of dehydroisoandrosterone sulfate decreases from 2 to 4 weeks before the blood pressure rises, and may reflect a decrease in placental blood flow, an abnormality known to be associated with preeclampsia and possibly related to fetal growth retardation and the fetal distress that sometimes occurs.[14] Neither of these tests is sufficiently accurate, and continued research is needed for the development of means for early detection of oncoming preeclampsia and for its differentiation from other hypertensive disorders.

The etiology of preeclampsia has been the subject of much research, but it remains unknown. Although uterine blood flow is considerably reduced in preeclampsia, the reduction may be an effect rather than the cause, for it also occurs in pregnant women with chronic hypertension. Nevertheless, the most popular hypothesis is that placental ischemia causes preeclampsia.[15] Experimental reduction

of the uterine blood flow in laboratory animals has been alleged to result in some, but not all, of the changes seen in preeclampsia. Repetition of the research has failed to confirm the original reports. A major difficulty in these studies is that too great a decrease in uterine blood flow damages the fetus; if the fetus survives, a collateral circulation is quickly established and may offset the initial reduction. Further research may reveal ways to circumvent these difficulties.

There is strong evidence for the hypothesis that a single recessive gene determines the development of preeclampsia and that every woman homozygous for the gene develops preeclampsia.[16] The hypothesis poses a problem, however, for it does not allow for known predisposing factors. Twin pregnancy, for instance, increases the incidence of eclampsia about 5-fold; fetal hydrops increases it 10-fold; and primigravidas are 8 times more susceptible to preeclampsia than are multiparas.[11] Research is needed to confirm or deny the genetic hypothesis and to reconcile it with the operation of predisposing factors.

Research on preeclampsia should focus on a subject population of primigravidas, preferably aged less than 25 years. Proteinuria should be a requirement for diagnosis, even though it is usually a late sign. Followup studies of women diagnosed as having had preeclampsia show that the prevalence of chronic hypertension is from 2 to 4 times higher in those who had no proteinuria than in those who did. In pregnancy, seemingly acute hypertension without proteinuria is often a manifestation of latent essential hypertension and is not preeclampsia. (The characteristic renal lesion of preeclampsia is almost never found in the absence of proteinuria.) Also, many women with antecedent chronic hypertension, even of severe degree, have normal blood pressures in midpregnancy, and when the pressure rises again in the 3rd trimester, the increase is often mistaken for preeclampsia.

Diabetes Mellitus

Untreated diabetes mellitus is incompatible with successful outcome of pregnancy. As treatment of diabetes has improved, pregnancy outcome has improved, but diabetes in pregnancy still constitutes a major problem in maternal-child welfare and requires further research. Presently, maternal mortality is similar for both diabetic and nondiabetic women, but maternal morbidity is higher in diabetics. By meticulous prenatal supervision and early delivery (mostly by cesarean section), perinatal mortality in diabetic pregnancy has been reduced to approximately 4 percent,

but not to the level of the general population.[17] Increased incidences of congenital anomalies, macrosomia, late intrauterine death, and respiratory distress syndrome (RDS) remain significant problems.

Pregnancy *per se* has a diabetogenic effect, and some women develop temporary abnormalities of carbohydrate metabolism, termed gestational diabetes; others may develop true diabetes during pregnancy. In both diabetes mellitus and gestational diabetes, the intrauterine environment is unfavorable for the developing fetus. Adverse outcome correlates directly with the severity of the maternal disease.[18]

With the development of tests that assess fetal maturity prior to scheduled delivery and of improved treatment for RDS, congenital anomalies and late intrauterine death are now the major problems for the fetus in a diabetic pregnancy. Research and treatment needs in the area have been summarized recently by the National Diabetes Advisory Board.[19] There is evidence that the decrease in perinatal mortality is attributable to better control of maternal blood glucose levels, and suggestions have been made that even more control from early pregnancy (or even before fertilization) might further reduce perinatal mortality and the incidence of congenital anomalies.[20,21] Studies to assess these possibilities are currently underway. Methods for achieving more physiological control of glucose levels by portable or internal insulin infusion pumps, transplantation of pancreatic islet cells, and other techniques should further improve glucose homeostasis during pregnancy. In conjunction with these studies, it is important to assess whether the neurological and developmental status of infants of diabetic mothers treated by these methods is different from the status of conventionally treated pregnant women with and without diabetes.

Despite advances in treatment, the pathogenesis of the fetal effects of maternal diabetes is still poorly understood. Abnormalities of amino acid, triglyceride, and fatty acid metabolism of the fetus have been identified, but how these or other abnormalities produce the fetal problems remains elusive.[20,22] Better understanding of such basic metabolic aberrations could lead to further improvements in treatment and outcome.

Infectious Diseases

Perinatal infections pose high risks for the fetus and newborn, but they are often manifest only by vague and nonspecific symptoms in the pregnant woman. Such diseases can be transmitted from mother to fetus by transplacental or

by ascending routes. In the first, a maternal bloodstream infection passes through the placenta, and in the second, which is more common, an inflammation ascends from the cervix. Fetal infections tend to occur near the time of delivery.

The fetus is dependent upon the mother to provide specific antibodies while it is developing its own host-defense mechanisms. The bulk of IgG antibodies in the fetus is maternal in origin, and it is the only type that is able to cross the placenta. Levels are low in the first 2 trimesters, but they increase rapidly in the last 3 months of gestation. Under normal conditions, IgG is found in amniotic fluid. Traces of IgA are also present, but IgM antibodies are absent. Around the 11th week of gestation the fetus is able to synthesize IgM antibodies, and an elevated IgM value in cord blood signifies fetal infection. Cellular immunity is present at birth, and the newborn has the capacity to express responses in vivo and in vitro. The development of the immunological system of the fetus, however, needs to be defined in more precise detail.[23]

A specific group of infections identified by the acronym TORCH (toxoplasmosis, other, rubella, cytomegalovirus, and herpes) represents a hazard for morbidity and mortality in the fetus and newborn. Between 1 and 5 percent of fetal malformations and a significant portion of deafness and mental retardation may be caused by these viral and parasitic infections. The fetal consequences seem to depend upon the maternal immunity to the infectious process, the gestational age at the time the infection occurs, and other factors not yet well defined.[24,25]

For ascending bacterial infections, intrauterine contamination may occur with intact or ruptured membranes. It has been observed that with their premature rupture, there is a marked variation in infant susceptibility to infection, which may reflect individual differences in local host-defense mechanisms. An antibacterial substance (zinc-protein complex) has been identified in the amniotic fluid. Although its role is unknown, its activity increases towards term.[26] More research is needed to characterize such substances, determine their role in protecting the fetus from infection, and assess their therapeutic potential.

The association of maternal acute symptomatic pyelonephritis with prematurity has long been recognized. In the late 1950s it was suggested that asymptomatic bacteriuria during pregnancy, which occurs in 3 to 5 percent of women, may also be associated with low birthweight and increased perinatal mortality.[27] Studies since then have been inconclusive, in part because they did not distinguish be-

tween infants that are premature by weight or dates and those that are small for gestational age. Nonetheless, evidence seems to support the association between bacteriuria, reduced birthweight, and increased perinatal mortality.[28] Furthermore, studies have suggested that treatment of the infection reduces the incidence of low birthweight in comparison to that in an untreated group.[29]

The mechanism by which infection affects prematurity is uncertain. One suggested possibility is that the bacterial infection retards placental growth and thus affects fetal growth.[29] Release of corticosteroids from the fetal adrenal in response to the infection, and release of prostaglandins from the infected membranes have also been suggested as being responsible for early initiation of labor and low birthweight. Other possibilities include effects of bacterial endotoxin, and depressed immunologic mechanisms either leading to or resulting from the infection.[30]

Another mechanism has recently been suggested by which either urinary tract infections or vaginitis could lead to premature labor and thus to an increased incidence of low birthweight.[31] The studies are based on the hypothesis that human labor is initiated by phospholipase A_2 contained in amniotic and chorionic membranes. This enzyme releases arachidonic acid from the phospholipids in the membranes, which in turn leads to the synthesis of prostaglandins. The prostaglandins stimulate uterine contractions of labor. Many of the bacteria responsible for maternal urinary tract infections, vaginitis/cervicitis, or intrauterine infection were found to be rich in phospholipase A_2 activity, and the phospholipase of these bacteria may serve as an exogenous source of the enzyme, which can lead to prostaglandin formation and thus to premature labor. This finding may explain, at least in part, the association of low birthweight with these infections.

Nutrition

The total dependence of the fetus on the mother suggests that nutritional problems of the mother may be reflected in the fetus. It is difficult, however, to identify a direct adverse impact. Acute caloric undernutrition of the mother may have little effect, as shown by studies of the offspring of women pregnant during the forced Dutch famine of 1944. Birthweight of these infants was only slightly reduced despite severe maternal caloric deficiency, and long-term studies have shown no adverse effect on their physical growth or intellectual function.

Chronic malnutrition poses a different situation, however, with offspring of such women generally smaller than

expected. There is a high incidence of low birthweight in developing countries, where protein-energy malnutrition is endemic, but it is difficult to assign a direct relationship between the two due to many other factors that may affect birthweight. Nonetheless, a number of intervention studies have shown a consistent, though small, increment in birthweight with supplemental feeding in pregnancy.[32] Behavioral effects due to nutritional deprivation during pregnancy alone have not been clearly demonstrated, although it has been shown that children whose mothers received food supplements during pregnancy and who themselves received supplements during infancy are more active and socially more participative in school than non-supplemented children.[33] Adverse cognitive effects have been reported in early childhood, but they become undetectable by school age.

Hematologic Disorders

Changes in the hematologic system during pregnancy involve blood volume, formed elements of cells, and the coagulation process. Total blood volume, mainly plasma, increases an average of 50 percent. Red blood cells increase 30 percent to accommodate the greater oxygen requirements of the mother and her developing fetus. The discrepancy between the increase in plasma and in red cells explains an initial fall in hematocrit values during pregnancy. For the mother, these two changes play a protective role against blood loss at delivery or decrease in blood pressure due to sequestration of blood in the lower extremities during the 3rd trimester. Still another change, a decrease in blood viscosity, facilitates the circulation of an augmented volume of blood. The white blood cell count increases slowly, with a peak value in the 30th week of gestation, and is accompanied by a concomitant heightened bactericidal activity. The platelets remain basically unchanged.

Anemia during pregnancy has an incidence of up to 20 percent in some populations, and is accompanied by higher perinatal morbidity and mortality.[34] Pregnant women with severe anemia suffer more complications, such as eclampsia and infections, and their infants are more frequently in the low-birthweight category.[35] The mechanisms responsible for these outcomes are not completely understood.

Maternal anemias may be nutritional in origin (deficiencies of iron or folic acid) or hemolytic (shorter red cell lifespan). The latter group includes patients with structural abnormalities of the hemoglobin molecule, such as sickle cell disease. These patients have an increased incidence of miscarriages and infections, and they produce

infants with intrauterine growth retardation.[36] No clear picture exists of the effects of various degrees of chronic anemia on the fetus or on the progress of pregnancy and labor. For the fetus, the safety and benefit of various schemes used in the treatment of maternal hemoglobinopathies, such as frequent transfusion for pregnant women with sickle cell anemia, remain to be determined.

Coagulation problems during pregnancy are rare disorders. When they are present, however, they are associated with a variety of complications, including placental separation, eclampsia, and fetal death.[37]

Malformations of the Reproductive Tract

Malformations of the maternal reproductive tract may have an impact on pregnancy by increasing the likelihood of fetal loss or of premature labor and delivery. The overall incidence of low birthweight in the offspring of patients with malformations of the reproductive tract is about 30 percent.[38,39]

The cause of abnormalities of size or shape of the uterus is generally unknown. Recent epidemiologic evidence has linked uterine and vaginal malformations to administration of diethylstilbestrol (DES) at the time the woman herself was developing in her mother's uterus ("DES daughters").[40] This treatment was provided in the 1940s in an attempt to prevent miscarriages in high-risk women. Two-thirds of women exposed to DES in utero have been found to have substantial changes in their uterus. The DES-exposed group has also had a significantly higher incidence of unfavorable outcomes of pregnancy than unexposed controls. Further study of the effects of DES and other agents is needed, along with research to overcome problems with pregnancy presented by such malformations.

Adolescent Pregnancy

The association of adverse outcomes of pregnancy during teenage years, for both mother and infant, came to national attention in the 1960s and 1970s. Epidemiologic data indicated that one-fifth of all births were to teenagers who, particularly at younger ages, had a higher maternal mortality rate, a 2-fold higher incidence of low birthweight infants, and 25 percent higher perinatal mortality. A number of studies have provided data indicating that, above age 15-16, much of this increased risk can be eliminated by early prenatal medical care. Below this age there seems to be inherent biologic risk to pregnancy for which even medical care cannot compensate.[41,42]

Research has been directed to the social consequences of teenage pregnancy. Data indicate that without intervention, 80 percent of women who deliver before age 18 do not finish high school, and 40 percent of those who deliver before age 15 do not finish 8th grade. One-third of pregnant teenage women become pregnant again within 18 to 30 months after their first childbirth.

Environmental Risk Factors

Over the last 40 years, increasing numbers of reports have appeared that link environmental factors and pregnancy outcome. These factors include drugs prescribed for maternal diseases, chemical pollutants in the atmosphere and in food, and radiation. They are important because of their adverse effect on the fetus. Toxic effects are not limited to anatomical malformations but may include biochemical, physiological, and(or) behavioral defects of varying degrees of severity. The concept that the maternal organism acts as a protective shield toward her fetus has been revised by the knowledge that although some substances are kept out, the majority of foreign compounds administered to the mother reach the developing organism and are distributed within it.

The ability of the fetus to dispose of foreign compounds changes throughout pregnancy. The most important route for excretion is the mother. Molecules that originally traversed the placenta to the fetus may be returned to the mother for appropriate elimination. Some chemicals may be unchanged; others, depending on the type of compound and stage of development of a particular fetus, may undergo enzymatic changes to a compound that is less or more toxic. The compound may interact with fetal receptors and produce an immediate effect, interfere with the ongoing process of growth and maturation, or be deposited in tissues or organs and be responsible for unexpected and(or) undesirable postnatal effects.

Drugs

Drugs given to the mother during pregnancy can also affect an immature and developing fetus. Observed effects include: masculinization of the female fetus by progestins metabolized into androgens; fetal hemorrhage and altered bone development induced by anticoagulant therapy; behavioral alterations in children caused by tranquilizers administered to the mother; adenocarcinoma of the vagina in young women exposed in utero to diethylstilbestrol; and teratogenic effects of drugs like thalidomide and hydantoin.[43-51] Of the large number of drugs that may be used

during pregnancy, only a few have been studied for safety during gestation.

In recent years drugs have been administered to treat the fetus rather than the mother. Technical advances in prenatal diagnosis and recognition of acute or chronic fetal diseases have made it possible to develop some effective therapeutic approaches.

The study of the metabolism of certain drugs has provided information regarding their capability for fetal enzyme induction. Phenobarbital, for example, was found to stimulate the activity of the glucuronide conjugation enzyme system in the fetus. This physiologic alteration has had therapeutic applications for the newborn with hyperbilirubinemia. Administering phenobarbital to the mother before delivery improves the infant's ability to metabolize bilirubin.[52] Intrauterine infections have been treated in the fetus with antibiotics, and pulmonary maturation (in order to prevent neonatal RDS) has been induced with steroids, thyroxine, and aminophylline. Many studies have evaluated the transplacental passage of antibiotics; some antibiotics have been found more effective than others, and some have toxic effects on the fetus.[53,54] Questions of long-term effects of prenatal steroid treatment remain unresolved.[55]

Alcohol Ingestion

Ethanol is a drug recently recognized as being hazardous to the developing fetus.[56,57] Excessive drinking during pregnancy may result in offspring afflicted by the fetal alcohol syndrome, whose main features include: pre- and postnatal growth deficiency in height, weight, and head circumference; brain dysfunction (often mental retardation); and a face that shows short palpebral fissures, small eyes, and small mid-area. The incidence has been calculated at about 1 per 1,000 live births, and the risk that the fetus will be affected is between 30 and 50 percent for a pregnant woman who drinks heavily. It is not clear if the toxic chemical that is responsible is ethanol *per se* or its breakdown product, acetaldehyde. As with other drugs administered during pregnancy, it is important to clarify the mechanisms that operate at various stages of development, the threshold dose, and the characteristics that may make an individual fetus susceptible.

Drugs of Abuse

Addiction in pregnant women is accompanied by drug dependency in the fetus. Withdrawal symptoms occur in fetuses and have been recognized as early as the 6th month,

coinciding with maternal symptoms. Neonatal withdrawal has been observed in nurseries. Medical or obstetrical complications also increase for the addicted mother. Nearly 50 percent of addicted women many suffer anemia, cardiac disease, hepatitis, hypertension, pneumonia, or veneral disease. Nearly half of such patients have had no prenatal care, and 10 to 15 percent have eclampsia and may deliver prematurely. Other obstetrical complications include early separation of the placenta, miscarriage, premature labor, and postpartum hemorrhage.[58,59] The exact role of the drug in these complications is not clear because of the difficulties in isolating the various confounding factors.

Smoking

A woman who smokes during pregnancy has an increased risk of giving birth to a low-birthweight infant. This relationship is independent of factors known to influence birthweight, such as race, parity, maternal size, socioeconomic status, and sex of the child. Several studies suggest that these children may have minimal but measurable deficiencies in their long-term intellectual development and behavioral characteristics. These findings need to be verified. Associations have also been found between maternal smoking and miscarriage, low implantation of the placenta and placental abruption, perinatal losses, and SIDS. The explanation for the effect of smoking may be related to intrauterine hypoxia.[60]

Radiation

In general, the developing human organism seems remarkably tolerant of low levels of ionizing radiation, as evidenced by the minimal effects on pregnancy of exposures at Hiroshima and Nagasaki.[61] Nonetheless, it is agreed that exposure should be kept to a minimum. Hazardous radioactive isotopes of iodine used in diagnostic imaging procedures[62] have been replaced by a safer compound, Technetium 99, from which the patient receives a much lower level of radiation. Radiological procedures are limited to patients for whom, after a risk-benefit evaluation has been undertaken, the procedures should not be postponed. The new physical diagnostic techniques, such as ultrasound, appear safe for both mother and fetus. Long-term followup studies, however, have not been completed.

Workplace Hazards

There is concern that occupational exposures to chemicals or toxic agents may result in miscarriage, malforma-

tions, or infertility. These exposures may not be limited to the workplace, since such chemicals can be carried on clothing from the workplace to the home. The health hazard may be greater to the developing fetus than to the mother, and effects may occur without warning signs or symptoms in the mother. The mechanism of action upon the fetus is similar to that of various drugs, and the hazards of many of these exposures are unknown.

Exercise

With an increasing proportion of women engaged in vigorous exercise, both as members of the work force and as participants in sports or fitness programs, the question of the effects of maternal exercise in producing fetal hypoxia becomes important.[63] These effects may be different in women who routinely exercise heavily and in those who do not. In the absence of evidence, some physicians recommend that pregnant women refrain from such activities as scuba-diving, long distance running, and mountain climbing, to avoid fetal hypoxia. Information is needed on how maternal physical exertion is tolerated by the fetus, and what restrictions of maternal activity are needed, if any.

Evaluation of Fetal Status

As described earlier, disorders of pregnancy as well as problems inherent in the fetus can adversely affect the fetus. During the last two decades, tests for assessing fetal status have been developed. Methods are being further developed that assess genetic makeup and physical intactness of the fetus, the extent of the influence of maternal nutrition problems on fetal health, the likelihood that the fetus can continue intrauterine existence safely, and its readiness for extrauterine existence.

Erythroblastosis Fetalis

In 1940, Hellman demonstrated the first successful prenatal fetal therapy by treating the mother with vitamin K during labor to prevent hemorrhagic disease of the newborn.[64] The first disorder for which both intrauterine diagnosis and fetal therapy were possible is erythroblastosis fetalis, or Rh hemolytic disease. A mother in this condition lacks the Rh antigen in her red blood cells (Rh negative), becomes sensitized to the Rh positive cells of her fetus, and produces antibodies to them. These anti bodies cross the placenta and destroy the fetal red blood cells. Anemia, jaundice, and hydrops fetalis result, and may

lead, in severe cases to fetal death or neonatal morbidity. In 1956, Bevis demonstrated successful use of transabdominal amniocentesis in the 3rd trimester to obtain an amniotic fluid sample for spectrophotometric analyis of bilirubin levels to assess how severely the fetus was affected.[65] Using this method of diagnosis to assess the need for treatment, Liley in 1963 developed the first direct intrauterine therapy, which was to treat anemia by the infusion of blood into the fetal abdomen by means of a long needle.[66]

Although these techniques are still in use, the development of Rh immune globulin (RhoGam) to prevent maternal sensitization (see below) has markedly decreased the incidence of this disorder and reduced the need for this procedure. The techniques themselves illustrate two major points: (1) the fetus is approachable as a patient and is amenable to therapy, and (2) accurate diagnosis is a necessary predecessor to fetal therapy.

Prenatal Diagnosis of Genetic Diseases and Congenital Defects

The severity, progressive nature, and lack of corrective treatment for many genetic disorders and congenital defects have caused parents and physicians to focus attention on their prevention. Prevention can be primary--that is, intervening before the condition develops; secondary--intervening after the abnormality exists but before it has adverse effects; or tertiary--avoiding permanent damage from the adverse effects.

The cause of many genetic diseases and congenital anomalies is not known, and thus how to approach their primary prevention is not known. Many etiologies, for example, have been suggested for neural tube defects (NTDs), which include anencephaly and spina bifida--such as eating blighted potatoes[67]--but the cause of this anomaly has not been identified. A vitamin deficiency has recently been suggested as a possible cause.[68] Multiple vitamins were administered prior to fertilization to 178 women at high risk who had a 5 percent statistical probability of having an affected infant. Only 1 infant (0.6 percent) was affected. Further trials of this promising primary preventive means are under way.

Other methods of primary prevention generally involve some form of avoidance. Certain drugs, such as thalidomide, are known to be teratogenic to the developing fetus and are thus to be avoided in pregnancy. The possible adverse effects on the fetus of most drugs, however, are unknown.

A successful example of avoidance of a teratogen is the syndrome of supravalvular aortic stenosis and mental retardation associated with high maternal vitamin D intake during pregnancy.[69] This syndrome seems to have almost disappeared with the restriction of vitamin D supplementation in the 1960s. For most foods and food additives, however, even more so than for drugs, safety for the fetus has not been studied or established.

Research in recent years has identified the basic defect for certain genetic diseases, and carrier detection for some of them has been made possible. Primary prevention of these disorders involves screening, either pre- or post-maritally. The broadest application of this preventive method has been in screening programs for Tay-Sachs disease and sickle cell anemia.[70]

In the past 15 years, researchers have been able to develop approaches involving various techniques for detecting fetal abnormalities in utero. The major techniques developed for prenatal diagnosis are amniocentesis, ultrasound, fetoscopy, and alpha fetoprotein screening.

Amniocentesis

Midtrimester transabdominal amniocentesis for prenatal diagnosis was developed in the late 1960s, following the demonstration that fetal cells in amniotic fluid can be grown successfully in tissue culture, for study of the chromosomes and enzyme activities.[71] By withdrawing 20 cc of amniotic fluid at around the 16th week of pregnancy, culturing the cells, and analyzing their chromosomes or a specific enzyme activity, it is possible to diagnose before 20 weeks gestation any chromosome anomaly, such as trisomy 21 or Down syndrome, and many metabolic disorders, such as Tay-Sachs disease. Since the initial intrauterine diagnosis of galactosemia in 1968,[72] it has become possible by amniocentesis to diagnose in utero approximately 100 genetic metabolic diseases. Studies of the accuracy and safety of this procedure have shown that diagnostic accuracy is in excess of 99 percent and that performing amniocentesis does not significantly increase the risk of fetal loss.[73-75] There is a slight risk to the fetus, since clear instances of fetal demise apparently caused by amniocentesis have been reported, but the frequency is probably less than 0.5 percent.[76]

Applications of amniocentesis for prenatal diagnosis have been extended recently by the use of gene probe techniques to diagnose disorders in fetal amniotic fluid cells that previously required a fetal blood sample. Sickle

cell disease is one example.[77] This technique holds great promise for diagnosing other disorders.

Amniocentesis has also made possible secondary prevention in the form of intrauterine treatment of a disorder before its adverse effects are manifest. Such prevention has been accomplished in the case of methylmalonic acidemia, by administering high doses of Vitamin B_{12} to the mother during pregnancy. The treatment was continued directly with the infant postnatally, and its growth and development have been normal, rather than the expected early disability and death.[78] Similar success has recently been achieved with prenatal treatment of congenital biotin dependency. Research may identify other disorders for which fetal treatment is possible.

Research is needed to broaden the applicability of amniocentesis. The underlying defect in some disorders, such as cystic fibrosis, must be known in order to make prenatal diagnosis possible, and recent progress in this effort has been reported.[79] Other diagnostic methodologies, such as cell fusion and spectrometry, hold promise. Use of amniocentesis would be enhanced by developing techniques to reduce the time required for cell growth in tissue culture and by improved automation of laboratory procedures and karyotyping. Cell sorting devices improved to select fetal cells from a maternal blood sample and provide prenatal diagnosis from these fetal cells without the need for amniocentesis could make it possible to offer prenatal screening for cytogenetic anomalies in all pregnancies. There is need for research directed toward identifying the pathogenesis and etiology of these disorders, and for development of improved methods of primary or secondary prevention.

Fetoscopy and Placental Aspiration

Fetoscopy involves insertion of a small fiberoptic endoscope through the abdomen into the uterus. The instrument permits direct visual examination of the fetus and fetal blood sampling by puncture of a fetal vessel on the surface of the placenta. Aspiration of a mixed maternal-fetal blood sample from the placenta can also be performed with a needle without using a fetoscope.

Visual inspection of the fetus makes possible the diagnosis of genetic diseases characterized by specific malformations, such as polydactyly of Ellis-van Creveld syndrome, and clarification of some anomalies, such as site and extent of a meningomyelocele.[80]

Obtaining a fetal blood sample makes it possible to diagnose hemoglobinopathies, such as beta thalassemia and sickle cell disease, and hematologic disorders, such as hemophilia, not diagnosable from amniotic fluid cells.[81] A fetal skin biopsy can also be obtained to diagnose other disorders.[82]

This technology, while in an early stage of development, has potential applications beyond prenatal diagnosis. By providing access to the fetal blood stream, it may permit the introduction of medicines, cell transplants, and even genetic material directly to the fetus, for treatment or correction of genetic disease or other developmental problems. Improvements needed for these applications, as well as for broader diagnostic use, are better instrumentation to provide a broader field of vision, the capability of cannulating fetal blood vessels, and reduced risk of the procedure for the fetus.

Ultrasound

An important advance in obstetrics during the past 20 years has been the use of ultrasound for viewing the fetus and placenta and for recording fetal heart rate. An outgrowth of the development of sonar for submarine warfare in World War II, its use in obstetrics was pioneered by Donald in Glasgow,[83] Sunden in Sweden,[84] and Holmes[85] and Hellman[86] in the United States. Present instruments provide images with a resolution of 2 mm.

Ultrasound has many capabilities in prenatal diagnosis of genetic disease and congenital defects. As an adjunct to amniocentesis, it can locate the placenta (so the needle can be directed away from it) and the fetal position, assess possible fetal death (by absence of fetal heart motion), diagnose multiple pregnancy, and measure biparietal diameter to date the pregnancy more precisely.[87-94] The latter is particularly important in studies of amniotic fluid alpha fetoprotein, discussed below. Ultrasound is also important as a diagnostic tool in its own right. It is extremely accurate in diagnosing anencephaly, and can detect internal and external structural defects, such as renal anomalies and meningomyelocele. Recently success has been reported in prenatal diagnosis of congenital heart disease.[81]

Ultrasound requires further improvements in instrumentation and refinement in operator techniques, to increase diagnostic accuracy and potential. No short term human safety hazards have been identified at the exposure levels used.[95,96] Systematic long-term human studies have not been performed, but present data suggest no hazard. Measurements of the amount of energy received by tissues would be useful to provide reassurance on safety.

Alpha Fetoprotein

Alpha fetoprotein (AFP) is a protein that is normally produced in fetal life. After that time production virtually ceases. Pregnancy is the only normal condition in which AFP is measurable above 1 or 2 nanograms per milliliter in adult serum; in this case it is made by the fetus and passes into the maternal circulation.

In 1972, it was determined that AFP levels were elevated in amniotic fluid in pregnancies in which the fetus had a neural tube defect (anencephaly, meningomyelocele, open spina bifida),[97] and later demonstrated that maternal serum AFP levels also were elevated in such pregnancies.[98] These discoveries made possible large-scale screening for this category of severe birth defects, which affects approximately 5,000 newborns each year in the United States. Metabolism and norms for AFP levels in amniotic fluid and maternal serum for each gestational week have been identified, and the assays have been simplified and are potentially available commercially.[81] Pilot studies have demonstrated the safety and limitations of the accuracy of the technology.[99-101]

As a screening procedure based on population norms, however, serum AFP is complicated by false positives and false negatives. Nearly all the false positives can be eliminated in the next stages of the screening process (repeat serum AFP, sonogram, amniotic fluid AFP), so that of 10,000 pregnancies screened by measuring maternal serum AFP, one or two normal fetuses will eventually be incorrectly diagnosed as having a neural tube defect (NTD).[102] Depending on the cutoff percentile used in the initial screen (serum AFP), about 10 to 15 percent of fetuses with an NTD will be missed. Moreover, fetal problems other than NTDs can elevate AFP levels.

Several supplementary tests have been studied in efforts to overcome the problem of false positives and false negatives in AFP screening. The tests showing most promise are amniotic fluid acetylcholinesterase, concanavalin-A non-reactive AFP, and D2-protein.[103-105] Further research to improve these tests, and a search for others to improve diagnostic accuracy, is of importance in refining screens for NTDs.

Neonatal Screening

For some disorders, screening in the newborn period rather than prenatally offers an opportunity for secondary prevention. The best known of these disorders are phenylketonuria and galactosemia. Diet therapy for them prevents the adverse effects from becoming manifest. Screening for

amino-acidurias is also done in some areas.[106] A highly accurate newborn screening program for congenital hypothyroidism has been developed, with treatment effective in preventing mental retardation.[107] Investigators have also identified other genetic disorders that can be diagnosed in the newborn period. Treatment for some, such as maple syrup urine disease and the urea cycle enzyme defects, is effective in preventing death or developmental disorders.[108,109]

Assessment of Fetal Growth and Position

The development of ultrasound also has permitted evaluation of fetal growth. Detailed norms have been established, as described above, that are useful in diagnosing intrauterine growth retardation (IUGR).[87-93] Typically, fetal body measurements become disparate from head size, which is unaffected until very late in IUGR. Making the diagnosis of IUGR is important for managing pregnancy, for assessing the effect of maternal disease on the fetus, and for anticipatory treatment of the infant at delivery and in the newborn nursery. Knowing that fetal growth is proceeding normally is reassuring in management of a complicated pregnancy. Ultrasound also permits easy diagnosis of multiple pregnancy, which is important for management as well as for distinguishing it from polyhydramnios when uterine growth seems excessive. It avoids the need for X-rays to make these diagnoses and thus eliminates a radiation hazard to the fetus. Fetal position also can be determined by ultrasound, to assist in managing labor and delivery.

Assessment of Fetal Maturity

Tests have also been developed to measure fetal biochemical and physiologic maturity. They are of particular importance in three major circumstances: (1) when labor begins prematurely; (2) when fetal problems are indicated by the results of tests of fetal well-being, and (3) when delivery is being scheduled, whether by induction or by cesarean, either electively or due to maternal disease.

A major risk involved in delivery before full maturity is that the infant will develop respiratory distress syndrome (RDS). In this disorder the lungs have not yet begun to manufacture sufficient surfactant to keep the alveoli from collapsing. Treating RDS is difficult, prolonged, and costly, and even with treatment, many severely affected infants die. The ability to determine whether surfactant is present is critical to timing of delivery.

In the early 1970s, biochemical tests became available to assess fetal lung maturity. These tests require a sample of amniotic fluid obtained by amniocentesis. One test, the lecithin/sphingomyelin ratio (L/S ratio),[110] measures the relative amounts of these phospholipids. A ratio above 2 appears around 36 weeks gestation and indicates the presence of sufficient pulmonary surfactant for neonatal lung function without RDS. Availability of this test has had a profound effect on obstetric practice, and potentially can eliminate the problem of iatrogenic prematurity.[81]

A simpler version of this test is the "shake test," in which the sample of amniotic fluid is diluted with saline, mixed with methanol, and shaken. The bubble formation at the air-liquid interface is observed and graded.[111] Although the test correlates well with the L/S ratio and is quicker and simpler to perform, it is less precise and less accurate.[81]

More recently the L/S ratio has been expanded to create the "lung profile."[112,113] This test improves the precision of the L/S ratio, particularly in diabetic pregnancies. Further refinements of this type of biochemical assessment of fetal maturity are under development.

Assessment of Fetal Well-being

Fetal Motion

Observing fetal motion has been made possible by the development of real time ultrasound. The most frequent application of this capability has been to determine whether or not the fetus is alive by assessing fetal heart motion. Ultrasound detection of fetal movement has also been used to evaluate fetal distress. Fetal breathing has been the most studied in this regard.[114,115] Some investigators have used a combination of fetal breathing, fetal motion, fetal heart rate, beat-to-beat variation, and amniotic fluid volume to predict fetal distress, and they have found that the combination reflects true fetal distress more accurately than any single factor.[116]

Fetal blood flow in the aorta and umbilical vein can also be measured by ultrasound. Studies using these measurements are important because changes in fetal cardiac output may be one of the best indicators of fetal distress. The search for other applications of ultrasound to assessing fetal distress is continuing.

Fetal Organ Function

The fetus and placenta produce increasing amounts of

estriol as a normal pregnancy progresses toward term. Estriol is the end-product of the convesion of cholesterol to dehydroepiandrosterone in the fetal adrenal, the 16-hydroxylation of that compound by the fetal liver, and the aromatization of 16-OH-DHEA to estriol in the placenta. Abnormal function in any of these organs may result in a reduced level of estriol in the maternal blood or urine. Investigators have found that a sudden decrease in urine estriol level during pregnancy or a very low value throughout pregnancy is associated with increased perinatal mortality.[117] Since this finding, other investigators have shown that the test of estriol level is helpful in evaluating the fetus.[118-121] Some studies suggest, however, that the high false positive rate of the test may too often lead to iatrogenic preterm delivery of normal fetuses.[122] Investigators are currently evaluating the use of measurement of unconjugated estriol in maternal plasma by rapid radioimmunoassay as an alternative screen for fetal organ dysfunction, to avoid the problems associated with 24-hour collections for urinary estriol measurements.

Fetal Heart Rate Responsiveness

The fetal heart rate may also be utilized to evaluate fetal well-being during the last trimester of pregnancy. Two techniques are most frequently used today. The first, the stress test (the oxytocin challenge test),[123] is based upon the fact that an oxygen-deficient fetus will respond to a further acute deficiency, created by a uterine contraction initiated by oxytocin administration, with a late deceleration of the fetal heart rate. In the hands of an expert, it has a very low false negative rate (3 per 1,000 fetal deaths within one week of a negative test). However, there is still an unacceptably high false positive rate.

The second antepartum fetal heart rate test for fetal well-being, the non-stress test, is based upon the fact that a normal fetus will have frequent heart rate accelerations associated with fetal movement.[124] This test is somewhat easier to perform than the contraction stress test and is probably the most frequently used method. The test has a low false negative rate (4 to 5 per 1,000 fetal deaths within one week of a reactive test) but a very high false positive rate.

A frequently employed approach is to use both the stress and non-stress tests, with the stress test performed only if the fetus is nonreactive during the non-stress test. The fetus may be nonreactive due to maternal drugs, fetal sleep states, hypoxia, and a variety of other factors. In this testing scheme, a major unanswered question arises as

to which test, stress or non-stress, gives a better indication of fetal distress.

Other, more reliable tests of fetal well-being need to be developed. One test that may fill this need but requires more technical and conceptual development is the electromechanical interval of the fetal heartbeat. Studies have shown that the interval is prolonged in chronic hypoxia.[125] The consistency of this finding and its clinical usefulness have not been demonstrated.

III. Birth

The time of labor and delivery presents two major potential hazards to the fetus: prematurity and birth injury. Prematurity is associated with over 60 percent of all infant deaths, and adverse occurrences during labor and delivery are estimated to account for 20 percent of stillbirths, 20 to 40 percent of cerebral palsy, and 10 percent of severe mental retardation.[81] Reducing these hazards requires research on the factors that maintain pregnancy and initiate labor, the normal and abnormal processes of labor and delivery, maternal and fetal responses to these stresses, and methods to detect and deal with abnormal responses.

Normal and Premature Labor

Maintenance of Pregnancy

The primary hormonal factors responsible for initiating and maintaining pregnancy have been established. Less clear is the role of other factors, such as relaxin. Studies have demonstrated that this hormone is elevated in plasma at the time of the first menstrual period missed after fertilization and that it suppresses spontaneous contractile activity of the human myometrium.[126] The mechanism of action of relaxin and the question of whether this mechanism is defective or whether hormone levels are inadequate in women with premature labor remain to be elucidated.

The chorioamniotic membranes also play an important role in maintaining pregnancy. Their premature rupture is a significant cause of premature delivery and infectious morbidity. Under normal conditions these membranes are stronger at preterm than they are at term. Studies have suggested that women whose membranes rupture prematurely have a defect in the strength of these membranes, and investigators have postulated further that such weaknesses might be due to environmental factors such as lead or other toxic substances.[127]

Initiation of Labor

Much of the research on the initiation of labor has been done in sheep. The mechanism of a rapid increase in cortisol levels, associated with an increase in estradiol and estrone and a reduction in placental production of progesterone just before labor begins, is well established.[128,129] The increase in estrogen stimulates placental production of prostaglandin F_2 . The decrease in progesterone may facilitate this response.[130] A relationship exists between prostaglandin and oxytocin. Oxytocin stimulates the release of prostaglandin, and prostaglandin increases the sensitivity of the myometrium to oxytocin.[130,131] One further effect of prostaglandin (E_2) in sheep is marked softening of the cervix.

The mechanism of labor in humans is less clear. There are higher levels of prostaglandins in the amniotic fluid of patients in spontaneous labor than in patients in induced labor.[132] Prostaglandin production requires a substrate, arachidonic acid. The phospholipids of the fetal membranes and decidua are rich in archidonic acid; however, to free this substrate the enzyme phospholipase A_2 must be present.[133] The amnion, chorion, and decidua contain this enzyme in the lysosomes.[134,135] The release of phospholipase A_2 from the lysosomes may be produced by the local withdrawal of progesterone, which had stabilized the lysosomes.[136] Other factors such as hypo- and hyperosmolar conditions also may cause lysosomal disruption.[137] In the rhesus monkey, injection of phospholipase A_2 into the amniotic cavity produces rapid cervical effacement and full dilation, accompanied by a marked rise in arachidonic acid levels.[138] Also, there is an increase in free arachidonic acid in the amniotic fluid during labor.[139] It has recently been shown that the principal sources of arachidonic acid are alkylacylphosphatidyl-ethanolamine (alkylacyl PE), diacyl PE, and phosphatidylinositol (PI) in amnion, and diacyl PE and PI in chorion.[140] Other investigators have shown that the prostaglandin synthetase activity in the amnion is greater after labor than before and that PGE_2 was formed in the amnion and chorion, whereas both PGE_2 and PGF_2 were formed in the decidua.[141]

Thus according to current concepts, labor begins when phospholipase A_2 is released from lysosomes in the chorionic and amnionic membranes. This enzyme cleaves arachidonic acid from phospholipids in the membranes. Arachidonic acid is converted to prostaglandins by prostaglandin synthetase. The prostaglandins then stimulate uterine contractions and labor. What remains uncertain is the normal trigger for phospholipase A_2 release from the lysosomes, as well as the abnormal triggers that may cause this process to start prematurely. One such potential abnormal trigger, an

exogenous source of phospholipase A_2 from bacteria, was discussed above. Demonstration of the role of this and other triggers may provide clues not only to the origins of premature labor, but to its prevention as well.

Arrest of Premature Labor

While there have been many attempts to stop premature labor with alcohol, beta agonists, magnesium sulfate, and prostaglandin synthetase inhibitors, none of these agents is completely efficacious or free of problems.[142-144] The success rate in stopping labor for 72 hours or more is about 80 percent, compared to 60 percent with a placebo. The problems with alcohol include: intoxication and vomiting; with beta agonists, maternal tachycardia, hyperglycemia and hypotension; with magnesium sulfate, magnesium toxicity; with both the latter, maternal congestive heart failure; and with prostaglandin synthetase inhibitors, pulmonary hypertension in the newborn.[145] A better tocolytic agent and a clear understanding of the causes of the onset of labor are needed.

Fetal Distress and Hypoxic Birth Injury

As noted above, intrapartum events can contribute significantly to perinatal mortality and morbidity. The mechanism for such injury most often is interference with the supply of oxygen to the fetus. That interference can occur abruptly and dramatically, as in prolapse of the umbilical cord or abruptio placentae, and can necessitate immediate emergency delivery if the fetus is to be saved. More often, the effects of fetal hypoxia during labor are more subtle. Passage of meconium and slowing of auscultated fetal heart rate are among signs used as indicators of this hypoxia. These signs have significant false-positive and false-negative rates, however, and investigators seeking a more reliable method of assessing fetal status during labor have turned to other methods.

Electronic Fetal Heart Rate Monitoring

The earliest method developed for assessing fetal heart rate is still in use, but it is by electronic equipment rather than the stethoscope and human ear, and monitoring is continuous rather than intermittent. Specific patterns of fetal heart rate change in association with uterine contractions have been identified and correlated with the events of labor and fetal status.[146-148] In particular, a pattern

has been shown of late deceleration of heart rate correlated with significant interruption of fetal oxygen supply. It is estimated that 60 percent of labors are monitored electronically.[81] While the majority of retrospective studies[149-150] and one prospective study[151] have shown a benefit to continuous monitoring, particularly in the high-risk patient, two recent prospective studies[152,153] have failed to demonstrate any benefit in the high-risk patient. All three prospective studies showed an increase in cesarean deliveries in the continuously monitored patient group.

The value of continuous heart rate monitoring was reviewed in the National Institutes of Health (NIH) Consensus Development Conference on Antenatal Diagnosis on March 5-7, 1979, sponsored by the National Institute of Child Health and Human Development (NICHD). In the Conference, it was generally agreed that continuous monitoring has value in the high-risk patient, but that its use should be optional in the low-risk patient. The need was emphasized for improved monitoring techniques to reduce the number of false positive indications of fetal distress. Other methods of alleviating fetal hypoxia before resorting to cesarean delivery were also urged.[81]

Other Methods of Fetal Monitoring

One adjunct to continuous electronic fetal heart rate monitoring is fetal scalp blood sampling to determine whether a fetus with an ominous heart rate pattern is in fact hypoxic and acidotic and thus at risk for brain damage or death. The technique uses a fetal scalp puncture to obtain fetal blood for pH determination.[154] A correlation of ominous fetal heart rate patterns and low fetal pH has been demonstrated in the human.[155] The extreme variability of the means requires several samples to determine whether the fetus is acidotic. One investigator has demonstrated that fetal scalp blood sampling reduces significantly the use of cesarean delivery for fetal distress.[153] Fetal scalp blood sampling has not yet achieved widespread acceptance because of lack of familiarity with the technique and lack of a micromethod blood gas laboratory in many hospitals.

There is a need for a continuously recording, reliable pH electrode that can be placed on the fetal scalp. Two problems have been observed in the available technology. The glass construction results in breakage, and long-term application may measure the pH of a surrounding hematoma more than the arterial pH. Such an electrode is currently available for testing and refinement,[156,157] and developing this technology should have a high priority.

Transcutaneous electrodes to measure pO_2 and pCO_2 have been developed and tested.[158] These electrodes have been of primary benefit in the management of the premature newborn infant in whom an oxygen tension that is either too low or too high can have serious consequences, but they have limited application in intrapartum fetal monitoring.

Safest Method of Delivery

When normal spontaneous vaginal delivery would be hazardous for mother or fetus, various interventions have been employed to improve outcome. Episiotomy, forceps delivery, version, rotation, and cesarean delivery are among the most common of these interventions, but there is uncertainty as to which procedures are necessary and which result in improved outcomes in specific circumstances. Of particular interest and concern is cesarean delivery.

The rate of cesarean delivery in the United States tripled between 1970 and 1978, from 5.5 to 15.2 percent. An NIH Consensus Development Conference on Cesarean Childbirth, on September 22-24, 1980, sponsored by the NICHD, identified four diagnostic categories responsible for 80 percent of cesarean deliveries, and urged that additional research be directed toward assessing whether cesarean delivery is the best way to deal with these obstetrical problems.[159] The four diagnostic categories were dystocia, repeat cesarean, breech, and fetal distress.

Dystocia includes both anatomic and functional problems that impede the normal progress of labor. Fetopelvic disproportion is a frequent contributor to this diagnosis. Malpresentations also lead to dystocia, and these infants probably benefit from cesarean delivery. Dysfunctional labor, however, appears to account for a greater portion of diagnoses of dystocia. (The term "dysfunctional labor" connotes abnormal progress in labor as determined by statistically derived criteria.[160,161]) There is epidemiologic evidence that prolongation of either the first or second stage of labor is associated with a higher perinatal mortality rate. The data indicate that for some patterns of dysfunctional labor, cesarean delivery improves outcome.[162] Data to substantiate this finding, however, are not available in other patterns of dysfunctional labor.[163] Interventions such as patient rest, sedation, hydration, ambulation, or oxytocin stimulation may relieve a dysfunctional labor without the need for cesarean delivery, but these issues require clinical study.

Cesarean delivery in the treatment of dystocia and malpresentations may not require as precise a pelvimetry as

does vaginal delivery, where exact measurements of pelvic shape and size are needed to prevent fetal damage. In spite of some preliminary research,[164] sonography has not proven successful in the measurement of transverse diameters and estimated shape of the mid-pelvis. Thus X-ray pelvimetry would have to be employed for these measurements, a technique that is not used extensively because of the fear of effects of radiation on the fetus. Modern X-ray machines and fast films have greatly reduced the radiation received by the fetus in X-ray pelvimetry. Research is needed to assess whether this reduction has so increased safety that pelvimetry may once again be a useful technique.

For many decades it has been standard medical practice in the United States (99 percent of cases) to deliver a woman with a previous cesarean by repeat cesarean, to avoid the risk of uterine rupture at the previous scar site. Recent studies have called this practice into question.[165] The scar from the low cervical cesarean incision now used is less likely to rupture than the scar from the classical cesarean operation previously in use, and a large proportion of women with a previous low cervical cesarean can apparently undergo a trial of labor and deliver vaginally with very low risk. Results of such deliveries should be monitored and studied so that factors associated with risk and success can be identified at an early stage.

With most repeat cesareans performed electively, prematurity and RDS become a concern. It has been observed that infants born by cesarean after onset of labor have a lower incidence of respiratory distress than infants of the same gestational age born by cesarean before labor begins. This phenomenon requires study to identify the factors responsible for the difference.

Regardless of the method of delivery, breech-presenting infants have a higher incidence of neonatal problems than cephalic-presenting infants. In the past decade the proportion of breech-presenting infants delivered by cesarean has risen from 12 percent to 60 percent. Among premature infants, cesarean delivery for breech presentation does not have a consistent relationship to survival, but those infants above 2,500 grams delivered by cesarean have a 5-fold better survival rate than those delivered vaginally.[159] Data are inconsistent, but suggest that despite the increase in cesarean rate, overall survival among breech-presenting infants has not improved during the last decade. Data to assess morbidity (particularly long term) in these infants are limited, but suggest that cesarean delivery reduces morbidity. It is important to collect both mortality and morbidity data by weight on this group of infants, comprising 3 percent of all births. The data should help in assessing whether cesarean or vaginal delivery provides the

best chance for intact survival and in identifing factors for determining the safest method of delivery.

IV. The Infant

During the past three decades, significant advances have been made in the diagnosis and treatment of disorders affecting the newborn infant, and neonatal mortality has been reduced. Achievements in perinatal research and major disease entities that are currently responsible for fetal and neonatal mortality and morbidity are discussed below.

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), or hyaline membrane disease (HMD), is the most common cause of respiratory distress in the premature infant. It is manifested clinically by respiratory insufficiency, and typical changes are present radiographically. The disease reflects lung immaturity and is caused by the lack of adequate amounts of surfactants (surface-active substances) to line the airspaces and prevent their collapse during expiratory movements. The role of surfactants was first described in the late 1950s.[166] Since then it has been shown clearly that a deficiency of surfactant synthesis because of prematurity is responsible for the disease. Research during the last 25 years has led to improved methods of diagnosis and management.[167-171]

The identification of various pharmacologic agents capable of inducing fetal lung maturation has led to prenatal maternal treatment with glucocorticoids for preventing RDS in the neonate.[172] Other agents, such as thyroxin[173] and aminophylline,[174] are also known to accelerate fetal pulmonary maturation. Clinical trials of these drugs are in progress and may provide further means of reducing the incidence of RDS. The potential long-term effects of fetal exposure to these agents are unknown and need to be examined.

A method of treatment developed in the 1970s and shown to improve ventilation and outcome for infants with RDS is continuous positive airway pressure to keep the alveoli from collapsing on expiration.[175] Several investigators have explored the physiologic basis for the use of assisted ventilation in infants with RDS and accounted for the significant improvement in the survival rates of those who are severely affected. Management of oxygen administration in treating these infants, both with and without ventilatory assistance, has been facilitated by the development of

transcutaneous pO_2 and pCO_2 meters. All of these measures have significantly reduced the case fatality rate of RDS during the last 20 years (table 8).

Other areas of current interest are the use of artificial surfactant and the potential use of high frequency ventilation for very severe RDS. Both uses have been successful in small groups of infants, but are still in the experimental phase.

The premature infant who develops RDS is dependent on supplementary oxygen and mechanical ventilation until there is adequate endogenous production of surfactant to stabilize the alveoli. In animal studies, natural surfactant instilled into the trachea was deposited in the airways, and it improved lung expansion and gas exchange.[176-178] Using mixtures of natural and synthetic (artificial) surfactant, investigators have recently shown similar but less consistent effects on human lung function.[178] These initial observations are sufficiently encouraging to warrant further clinical trials. If this mode of therapy can be perfected, survival should improve and the chronic long-term effects of oxygen and positive pressure ventilation on the developing neonatal lung may be minimized or prevented.

Recent observations in animals[179] and humans[180,181] suggest that high frequency ventilation (rapid oscillation ventilation) in the range of 15 to 20 cycles per second may be a reasonable alternative to conventional intermittent mandatory ventilation or continuous positive airway pressure breathing. The major advantage of high frequency ventilation appears to be the lower peak pressures needed for gas exchange and the resulting lesser potential for complications.

Symptomatic patent ductus arteriosus (PDA) and bronchopulmonary dysplasia (BPD) are emerging as the two most common adverse sequelae of RDS. These complications are particularly common among low birthweight infants. The precise mechanism for the development of symptomatic PDA is still unknown. The presence of a PDA may be a contributory factor in the development of BPD. The present methods of closure of a PDA are either surgical (ligation) or pharmacological (administration of a prostaglandin synthetase inhibitor, Indomethacin).[182] Recent investigations have demonstrated that antenatal glucocorticoid administration is associated with a decreased incidence of significant PDA in preterm infants, although the exact mechanism has not been elucidated.[183,184]

The major long-term adverse consequence for infants requiring prolonged ventilatory assistance is a type of chronic obstructive lung disease. It has been labeled

TABLE 8. Trends of Case Fatality Rate in Neonates with Respiratory Distress Syndrome

Series	San Francisco*			Montreal**			San Antonio***		
Birth-weight (grams)	1,000 -1,500	1,501 -2,000	≥ 2,000	1,000 -1,500	1,501 -2,000	≥ 2,000	1,000 -1,500	1,501 -2,000	≥ 2,000
1960s	85%	35%	40%	52%	39%	39%	—	—	—
1969-70	40%	22%	25%	—	—	—	—	—	—
1975-76	15%	0	0	—	—	—	23%	6%	1%

Sources:

* Tooley, W.H.: Hyaline membrane disease. Am. Rev. Respir. Dis. 115: 19-28, 1977.

** Usher, R.: Reduction of mortality from respiratory distress syndrome with early administration of intravenous glucose and sodium bicarbonate. Pediatrics 32: 966-975, 1963.

*** Corbet A.J. and Adams, J.M.: Current therapy in hyaline membrane disease. Clin. Perinatol. 5: 299-316, 1978.

bronchopulmonary dysplasia. The term indicates the chronic changes seen at the alveolar level and in the smaller airways and bronchioles.[185] It is usually seen in preterm infants who require mechanical ventilation for severe RDS, and it develops in 10 to 20 percent of such infants. The two foremost causes of BPD appear to be: oxygen toxicity to the developing lungs, which leads to pulmonary fibrosis; or pulmonary trauma by positive pressure ventilation, which causes a proliferative obliterative bronchiolitis.

The infant who develops BPD commonly requires intensive care for 1 to 2 months following birth and is frequently readmitted for recurrent respiratory illness in the first year of life. The disease is occasionally associated with a degree of right heart failure secondary to the pulmonary pathology (cor pulmonale), which also requires treatment. Present research pertaining to BPD is concerned with the use of pharmacologic agents, including diuretics, Vitamin E as an antioxidant,[186] and aminophylline as a bronchodilator,[187] in attempting to avoid the development of the condition.

Neonatal Infections

The newborn infant is susceptible to many infections, ranging from mild inapparent infections that need no treatment, to overwhelming sepsis (bacteremia). Prior to the discovery and development of antimicrobial agents, infection accounted for a very large number of neonatal deaths. The availability of these antimicrobial agents has reduced the fatality rate, but septicemia remains a significant cause of infant mortality and the only cause that is increasing. Advances other than antimicrobials include: new information on developmental immunology, demonstrating that the relative increase in susceptibility to infection of premature infants is explained by immaturity of their immunodefense system; and new knowledge of the source and route of neonatal infection, as illustrated by the close relationship between maternal acquisition of Group B streptococcal infection and the development of neonatal Group B streptococcal sepsis.[188-189]

Regardless of the infecting organism, neonatal sepsis occurring in the first days of life usually appears as respiratory distress, and the clinical manifestation is often indistinguishable from RDS. The disease is rapidly progressive and carries a 50 to 70 percent mortality rate. Early diagnosis and prompt treatment are important. Improved means of diagnosis are needed to lower the mortality rate.

Advances in the management of neonatal sepsis have included use of new antibiotics and exchange transfusions. Preliminary reports speculate that beneficial response to the latter may be due to removal of endotoxins, improved cellular and humoral immunity, and replenishment of clotting factors.[190] Controlled studies are lacking and further study into the proposed mechanism of action is needed. Since many infants with this form of neonatal sepsis are leukopenic and neutropenic (low white cell counts), the use of leukocyte transfusion has been tried with some success.[191]

Recent observations have indicated that chlamydial infections, besides causing conjunctivitis in the neonatal period, may also produce a distinct respiratory disorder characterized by an afebrile course, tachypnea, chronic diffuse lung involvement, and elevated serum immunoglobulin (IgG and IgM) levels.[192] A pilot study has shown that about one-half the neonates exposed to chlamydia will develop conjunctivitis and that an estimated 2 to 6 percent of all newborns are likely to be affected. The contribution of Chlamydia trachomatis to neonatal respiratory distress is unknown. The source of the organism is thought to be the maternal genital passage. An epidemiological assessment of the incidence and spectrum of the disease is needed. Questions to be addressed include whether therapy is indicated in all cases of ocular and pulmonary involvement since tetracycline, the usual drug of choice, is contraindicated in the neonate; and whether an infant with pulmonary disease poses a public health risk for other patients in the hospital setting.

Virus infections such as rubella, herpes, and cytomegalovirus (CMV) do not occur frequently, but their results can be devastating in pregnancy or to the newborn. Some of the long-term consequences of these infections are known; others, such as learning disorders with CMV infection, are just coming to light.[193]

Many of the infections that the fetus acquires from the mother are sexually transmitted (CMV, herpes, and chlamydia, for example). The rising incidence of sexually transmitted diseases makes this area important for study.

Infant botulism has been identified as a distinct clinical entity. It is caused by Clostridium botulinum and has been reported in infants between the ages of 3 weeks and 7 months. It is a complex syndrome manifested by a broad clinical spectrum, extending from asymptomatic carriers, to varying degrees of neuromuscular weakness, to more fulminant cases with respiratory arrest and death.[194] Diagnosis is made by demonstration of toxin or organisms and

by characteristic electromyographic changes. Current therapy involves supportive intensive care. Needed research on this disease includes differentiation of pathogenesis between "toxin-ingestion" as opposed to "toxin-infection" mechanisms,[195] the usefulness of antibiotics directed toward the treatment of intestinal C. botulinum, and the possible role of botulism in the sudden infant death syndrome.[196]

Erythroblastosis Fetalis and Bilirubin Encephalopathy

Approximately 1 percent of all deliveries are affected by erythroblastosis fetalis.[197] About 98 percent of these are ABO blood group incompatibilities and have little clinical significance. The 2 percent of erythroblastosis fetalis cases attributable to other factors, particularly the Rh factor, contribute most of the problems. Until the mid 1960s, Rh erythroblastosis accounted for significant perinatal mortality, neonatal morbidity, and long-term sequelae (deafness, mental retardation, cerebral palsy). The development of anti-Rh globulin and treatment of the mother with this preparation (RhoGam) after delivery have markedly reduced the incidence of Rh isoimmunization. The remaining problems that need to be addressed are: maternal sensitization following abortion and amniocentesis; underutilization of RhoGam after delivery; failure of RhoGam due to maternal sensitization prior to delivery; and presence of non-Rh antibodies such as E, C, Kell, and Duffy. Clinical trials to assess the value of routine Rh prophylaxis in women at risk between 28 and 34 weeks gestation may be needed. Development of improved methods of quantifying volume of fetomaternal hemorrhage would help to assess the most appropriate dose of RhoGam.

Bilirubin encephalopathy, or kernicterus, is a complication of hemolytic disease of the newborn, and it is also a threat to premature infants who cannot remove bilirubin rapidly enough due to their immaturity. It develops when bilirubin, the yellow pigment produced from the hemoglobin in red blood cells, crosses into the central nervous system and injures the brain, particularly the basal ganglia. The true incidence of bilirubin encephalopathy cannot be assessed accurately because the signs are nonspecific. The only certain diagnosis of bilirubin encephalopathy is based on postmortem examination.

Treatment of the jaundiced (hyperbilirubinemic) infant is directed toward lowering the level of bilirubin or keeping it from entering the brain to prevent kernicterus. Measures employed have included hydration, administration of albumin, drugs to stimulate liver enzymes to speed bilirubin excretion, and when these have failed, exchange transfusion

to physically remove bilirubin along with the serum and the damaged red blood cells. In 1968, phototherapy to treat or prevent jaundice due to Rh disease or to prematurity was introduced in the United States.[198] Its use has become widespread, and it has markedly reduced the need for exchange transfusion and has probably reduced the incidence of kernicterus.[199] Its long-term safety is currently under study.

In term infants, kernicterus usually does not occur until the concentration of unconjugated bilirubin in serum exceeds its binding capacity (to albumin), a level estimated to be around 20 to 25 mg per 100 ml. Two recent studies suggest, however, that kernicterus may occur in the low birthweight infant at peak bilirubin levels as low as 6 to 10 mg per 100 ml.[200,201] In these studies, factors previously thought to increase the risk of kernicterus (hypothermia, hypoglycemia, infection) had no such effects, although the effects of other risk factors (acidosis, hypoalbuminemia, and low bilirubin binding reserve) were questionable. Further studies are needed to delineate the risk factors for kernicterus, to develop clinical means for the diagnosis of bilirubin encephalopathy in the low birthweight infant, to develop improved measures of bilirubin binding capacity, and to assess treatment modalities in well-controlled clinical trials.

Extreme Prematurity

Prematurity refers to delivery prior to 37 weeks of gestation or to a birthweight below 2,500 grams. Among newborns weighing less than 2,500 grams, two-thirds are born early and one-third are full term and small for their gestational age. Approximately 7 percent of all births fall into the low birthweight group, and 1 percent are very low birthweight (below 1,500 grams).

The problems of the premature infant are due in part to immaturity of vital organs and in part to disorders to which they are particularly susceptible. Respiratory distress due to lung immaturity often requires prolonged ventilatory support. Total intravenous nutrition may be needed until the stomach capacity enlarges and permits enteric feedings, initially by tube. The premature infant is very vulnerable to infection and often needs antibiotic treatment. Fluid and electrolyte management is precarious because of immature kidney function, and as a consequence the infant is easily overloaded with salt and water. The diseases that are special threats include necrotizing enterocolitis, retrolental fibroplasia, hyperbilirubinemia, intraventricular hemorrhage, and patent ductus arteriosus. Apneic spells (cessation of breathing) require constant monitoring and frequent resuscitation. The infant who is small for gesta-

tional age has a low tolerance for the asphyxia of labor and delivery. There is also an increased risk of stillbirth, severe perinatal asphyxia, hypoglycemia, polycythemia, meconium aspiration, and pulmonary hemorrhage.

The quantity and quality of the major nutrients necessary for parenteral nutrition of the premature infant are generally well established, but the requirements for vitamins, essential fatty acids, and trace elements are not clearly defined, particularly in infants who require a prolonged period of nutritional support. Issues involving the avoidance and treatment of complications resulting from parenteral nutrition, such as hyperglycemia, volume overload, metabolic acidosis, liver damage, and hyperammonemia, need to be investigated.

The improvement in survival, based upon utilization of newer diagnostic and therapeutic capabilities in intensive care nurseries, is mainly limited to prematures weighing above 1,000 grams at birth. Infants below 1,000 grams continue to have a high mortality rate, and the survivors suffer many disabilities that develop as sequelae of intraventricular hemorrhage, apnea, asphyxia, chronic lung disease, and other conditions. Of infants below 750 grams, fewer than half survive, and a significant number have continuing problems as a consequence of their early complicated medical course. Studies are needed to define factors leading to the initiation of both term and premature labor, as well as studies of problems occurring more frequently in the premature infant.

Intracranial Hemorrhage

With improved obstetric and neonatal care, intracranial hemorrhage due to birth trauma has decreased, but hemorrhage associated with asphyxia and prematurity has become more common.[202-204] The full-term infant is at risk for subarachnoid and intracerebral hemorrhage following hypoxic-ischemic encephalopathy and birth asphyxia. The preterm infant is prone to periventricular and intraventricular hemorrhage, frequently in association with severe respiratory distress syndrome.[205] The association with prematurity seems to be related to several factors: the presence of a specific area of the brain (subependymal germinal matrix around the caudate nucleus), which prior to term provides weak support to small vessels; the type and state of arterial and capillary development in the brain; and a physiological impairment in vascular autoregulation.

The recent availability of noninvasive imaging techniques using computed axial tomography (CAT scan)[206] and ultrasonography[207] has provided greater insight into the

true incidence and evolution of intracranial hemorrhage. The reported incidence of intraventricular hemorrhage using these techniques in infants below 1,500 grams birthweight ranges from 40 to 82 percent. The long-term outcome of infants with intracranial hemorrhage appears to be related to the degree of hemorrhage and the presence of complications.[208] Post-hemorrhagic hydrocephalus is seen in many of the survivors, and the severity of developmental and neurologic handicap correlates with both the presence of hydrocephalus and the degree of hemorrhage.

Further work needed in this area includes studies of the factors influencing the perinatal cerebral circulation, the role of obstetric and postnatal procedures in the pathogenesis of hemorrhage, and improved imaging techniques and noninvasive biophysical techniques to monitor cerebral circulation and intracranial tension.

Persistent Fetal Circulation

Persistent fetal circulation, also known as persistent pulmonary hypertension of the newborn, is a disorder characterized by central cyanosis and a variable degree of respiratory distress with an onset usually within 24 hours after delivery. The predominant circulatory changes are a decrease in pulmonary blood flow with a right-to-left shunt through the ductus arteriosus and foramen ovale (persisting fetal channels). To date it has been described both as an isolated entity, apparently triggered by perinatal hypoxia, and as a complication of a variety of disorders, including diaphragmatic hernia, meconium aspiration syndrome, polycythemia, and Group B streptococcal infection.[209] The exact etiology and pathogenesis are unknown. It usually occurs in full-term infants born following complications of pregnancy, labor, and delivery. The incidence has been estimated at 1 in 1,500 live births.

The management of this condition with the use of pulmonary vasodilators such as tolazoline has been only partially successful.[210] The overall mortality is 20 to 30 percent and is higher in infants who do not respond to vasodilator therapy.[210,211] Future studies are needed on noninvasive methods to diagnose pulmonary hypertension and myocardial dysfunction, such as echocardiography, and on the evaluation of pharmacologic agents having specific action on the pulmonary vasculature, such as pulmonary vasoactive prostaglandins.

Necrotizing Enterocolitis

Necrotizing enterocolitis is a disease of newborn infants characterized by intolerance of feeding, abdominal

distention, bloody stools, and pneumatosis intestinalis (gas in the bowel wall). The disease may progress to perforation of the bowel and require surgical intervention. Survivors are at increased risk for delayed growth and development. Contributory factors to the delays include nutritional deprivation, extended periods of parenteral nutrition, prolonged traumatic hospitalizations, and strictures of the bowel.

The etiology is unknown but is thought to be related to the introduction of feedings into a bowel injured by ischemia from perinatal stress, such as asphyxia or hypothermia, and colonized by hospital-acquired bacteria. More than 95 percent of cases occur after the introduction of feedings. The incidence is 1 to 2 cases per 1,000 live births. It occurs 10 times more frequently in infants weighing less than 1,500 grams at birth than in infants weighing more than 2,500 grams. Perinatal factors do not identify the infants at risk, except by birthweight or gestational age. The infant at highest risk is premature, has been fed, and has had some perinatal stress. Treatment is entirely palliative, although some studies have suggested that prophylactic antibiotic treatment may reduce the incidence.[212]

Research is needed: to develop ways to assess the mucosal and vascular integrity of the bowel prior to the onset of feedings; to improve methods of providing caloric requirements without increasing the risk of the disease; and to evaluate the benefit in using enteral antibiotics or fresh breast milk to control the neonate's bowel flora and prevent the disorder.

Metabolic Disorders

There are a number of metabolic complications during the neonatal period that carry significant risks for developmental and neurological complications. Examples include hypoglycemia (more commonly seen in preterm and infants small for gestational age and present in 5 to 10 percent of those with birthweights less than 2,500 grams) and hypocalcemia (incidence of 30 percent in preterm infants with birthweight less than 2,000 gms). These disorders have been studied, and methods for detection and management are established. Polycythemia (central venous hematocrit exceeding 65 percent) and concomitant hyperviscosity have recently generated interest because of the potential effect on cerebral blood flow and consequent adverse developmental effects. Long-term studies are needed of the outcome of infants who develop polycythemia.

Neonatal Pharmacology

The treatment of diseases in the newborn, whether full term or premature, often requires the administration of drugs. Prior to availability in the nursery, drugs are tested in adults, and the appropriate dosage and indications are derived from accumulated experience. Infants in the neonatal period, however, can suffer from disorders specific to their age group with no counterpart in the adult population. Some of these have been described above. Use of drugs in these disorders requires testing in affected infants to determine dosage, efficacy, and safety. This testing, as well as routine drug use, is complicated by the fact that the newborn, either full term or premature, is undergoing continuous changes in function (maturation) while adapting to a new extrauterine environment without the possibility of utilizing an adult organism (the mother) for the transformation and elimination of drugs. In addition to drugs administered directly, infants may carry foreign chemicals received in utero when administered to the mother. Studies in drug disposition, pharmacokinetics, and drug effects in the newborn are beginning to show the complexity of the problem and the need to expand research in this aspect of neonatal care. It is important to clarify interactions between medications, physiologic events in newborn infants (especially prematures), and specific diseases.

V. Research Recommendations

Certain problems of major impact should be pursued. Among these, top priority should be assigned to prematurity, second priority to perinatal asphyxia, third to congenital malformations, fourth to infections of the newborn and mother, and fifth to birth trauma.

General research needs that apply to the entire field of perinatal medicine are these:

- A basic understanding, at the molecular and cellular level, of problems affecting pregnancy and the newborn should be developed. Akin to these studies is a need for knowledge of normal fetal and newborn physiology such as control of blood volume and circulation, maintenance of respiration, and maturation of renal function.

- New forms of diagnosis and therapy that are being developed should be evaluated for efficacy and possible hazards through well-constructed randomized controlled clinical trials.

- As more infants of younger gestational ages survive, in-depth followup studies should be undertaken to determine potential or actual biologic or psychosocial problems.

- There should be controlled prospective trials to evaluate not only new pharmacologic treatments for various diseases in pregnancy and inhibition of labor, but also the safety and efficacy of the technologic developments being used to assess the fetus during pregnancy and labor, as well as the newborn infant.

- There is a need for work to further reduce the volumes of blood needed for tests.

- New and improved animal models need to be developed for the study of many of these disorders.

Pregnancy

- Determine the mechanism(s) responsible for the development of preeclampsia, test the various theories regarding its origin, and develop methods to improve the timing and accuracy of diagnosis to distinguish it from other causes of hypertension in pregnancy, and develop and assess improved methods of treatment.

- Determine the mechanism for the increased incidence of congenital malformations in diabetic pregnancies and assess prospectively the effect of early and rigid control of maternal blood glucose levels on reducing the incidence of malformations; assess the effectiveness of new methods of glucose control on pregnancy outcome; determine the cause of gestational (Class A) diabetes, and assess the extent to which routine screening for this disorder will reduce fetal mortality and morbidity; assess the safety of term labor and vaginal delivery rather than scheduled cesarean birth in controlled diabetic patients, and develop improved methods for assessing fetal lung maturity to reduce the inaccuracies of the L/S ratio in the diabetic patient.

- Determine the mechanism by which the fetus is affected by maternal infections, including the route and the pathogenesis, particularly with respect to genitourinary and TORCH infections; assess the accuracy and benefits of diagnosis during pregnancy of possible TORCH infections; and assess the mechanisms that normally serve to protect the fetus from

infection, and the possible role of defects in these mechanisms in the pathogenesis of the infection. Additionally, evaluate the safety and efficacy for mother and fetus of antimicrobial treatment of maternal infections and assess the role of maternal genitourinary infections in reducing birthweight due to IUGR, premature labor, or both.

- Assess the effects of maternal diet (calories, nutrients, and additives) before and during pregnancy on fetal growth and development and on maternal disorders of pregnancy.

- Improve prenatal diagnosis of fetal hematologic disorders, and improve methods to help women with hematologic disorders to have a successful outcome of pregnancy.

- Develop improved methods to manage problems posed to successful pregnancy outcome by malformations of the maternal reproductive tract.

- Assess the biologic impact on mother and infant of adolescent pregnancy, and develop and test the effectiveness of interventions designed to avoid adverse outcomes of pregnancy in this age group.

- Assess the effects on mother and fetus of exposure during pregnancy to drugs (prescribed, over-the-counter, and drugs of abuse), possible teratogens (including alcohol and radiation), smoking, exercise, and workplace hazards. Assessment should emphasize the cellular effects of these substances, the role of the placenta as a toxifying and detoxifying agent, the effects at different stages of gestation, determination of a safe dosage or exposure level, the role of genetics or cofactors in the manifestation of or protection from adverse effects, and assessment of long-term as well as short-term hazards.

- Expand the applications of amniocentesis by such means as identifying specific metabolic defects, gene probe techniques, and improved carrier detection, and improve the laboratory methodologies associated with amniocentesis by devising means to induce more rapid cell growth in tissue culture and by automation.

- Develop improved methods of obtaining fetal cells from a maternal blood sample to broaden the availability of prenatal diagnosis without the need for amniocentesis.

- Improve the safety and the instrumentation of fetoscopy to broaden the visual field and facilitate cannulation of fetal vessels, and expand the applications of fetoscopy to other disorders.

- Improve diagnostic capabilities of ultrasound for congenital defects, placental pathology, and other fetal abnormalities, and develop methods of assessing dose received by the fetus in ultrasound procedures.

- Develop and assess the effectiveness of methods designed to increase the diagnostic accuracy of alpha fetoprotein screening for neural tube defects, evaluate the wide-scale application of maternal serum alpha fetoprotein screening, and search for other prenatal markers for congenital defects.

- Continue to refine fetal measurements useful in diagnosing and following the course of intrauterine growth retardation.

- Continue refinement of the "lung profile" to assess fetal lung maturity; evaluate its accuracy, particularly in diabetic pregnancy, and attempt to identify other markers of maturation of other fetal organ systems.

- Evaluate the accuracy of present methods of assessing fetal well-being, and develop new and improved methods for such assessment.

- Develop and evaluate the safety and efficacy of methods for the prenatal treatment of fetal disorders.

Birth

- Evaluate the roles of hormonal factors, such as relaxin, and of mechanical factors, such as membrane strength and uterine muscle activity, in maintaining normal pregnancy and in initiating premature labor.

- Identify more specifically the mechanism(s) responsible for normal initiation and progress of labor in the human, and evaluate mechanisms proposed as being responsible for premature initiation of labor, with primary attention given to the role of maternal genitourinary infections as an exogenous source of phospholipase.

- Evaluate the efficacy and safety of beta agonists in arresting premature labor, and develop other means to arrest premature labor safely for mother and fetus.

- Develop adjunctive measures that will confirm or refute the diagnosis of fetal hypoxia suggested by electronic fetal heart-rate monitoring to reduce the high incidence of false positives, and develop improved methods for diagnosing fetal well-being and distress as suggested by electronic fetal monitoring, with special emphasis on the scalp pH electrode.

- Evaluate the outcomes, both short-term and long-term, of pregnancies with various complications of labor, in relation to the method of delivery.

- Develop a safe and effective method for preterm initiation of labor when delivery is necessary, as an alternative to cesarean delivery.

The Infant

- Develop and assess improved treatment adjuncts to reduce the incidence of complications of respiratory distress syndrome (RDS) and of its therapy, and assess the efficacy and safety of new modes of therapy for RDS.

- Develop methods for earlier diagnosis of neonatal sepsis, determine the pathogenesis of Group B streptococcal sepsis, and explore improved methods for preventing and treating neonatal sepsis.

- Develop methods of preventing the adverse effects on the infant due to prenatal maternal viral and parasitic infections.

- Expand the study of the pathogenesis and effects of perinatal chlamydia infections, including epidemiology and appropriate therapy.

- Determine the pathogenic mechanism and epidemiology of infant botulism and the role of antibiotics in its treatment.

- Characterize further the ontogeny of the immune system in the newborn infant and its relation to perinatal infection.

- Assess the value of routine RhoGam prophylaxis for

Rh negative women at approximately 28 weeks gestation.

- Determine the appropriate dosage of RhoGam to be given after midtrimester amniocentesis.
- Develop improved methods to quantify the volume of fetal-maternal hemorrhage and determine whether it should influence the dose of RhoGam.
- Develop and assess the accuracy and usefulness of improved methods for measuring reserve bilirubin binding capacity in the newborn infant.
- Develop agents that can be administered to the infant to bind and remove bilirubin.
- Identify the factors that determine development of kernicterus at lower bilirubin levels in premature infants.
- Complete the assessment of the long-term effects of neonatal phototherapy.
- Assess the long-term outcomes for premature infants by specific weight groups in relation to various neonatal disease entities, diagnostic procedures, and treatments.
- Determine the factors that influence perinatal cerebral circulation and the role of obstetric and postnatal procedures in the pathogenesis of intracranial hemorrhage, improve methodologies for diagnosing intracranial hemorrhage and for monitoring cerebral circulation and intracranial pressure, and develop and assess the efficacy of improved methods for treating intracranial hemorrhage.
- Determine the pathophysiology and long-term complications of persistent fetal circulation, especially its relationship to perinatal hypoxia; develop more effective methods of noninvasive diagnosis and treatment of persistent fetal circulation.
- Conduct epidemiologic studies of necrotizing enterocolitis, with special attention to its relation to time and type of feeding; identify the pathogenesis of this disorder; develop improved methods of prevention and treatment; and assess the long-term effects of necrotizing enterocolitis on bowel function.
- Develop improved methods of screening, diagnosis, and treatment of metabolic disorders.

- Assess differences in metabolism, disposition, and effects of pharmacologic agents by the newborn infant at various ages and weights, and evaluate the safety and efficacy of specific drugs, especially antibiotics, bronchodilators, and cardiovascular drugs, used in treating newborn infants.

- Determine the optimal composition for total parenteral nutrition for newborn infants of various weights and gestational age.

- Assess the value of breast milk in feeding small premature infants, the immunologic and psychologic benefits of breast feeding, and the extent and risks to infants of contaminants in breast milk.

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